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The stress fracture is one of the most frequent injuries in peacetime military populations, responsible for the military's greatest drain of both lost recruit time and medical resources. Unfortunately, not until we improve our understanding of the causative agents of this pathology can we expect to take effective measures in diminishing its appearance. Thus far, the studies we have undertaken have demonstrated that the origins of the lesion stem from tissue remodeling, to material microdamage. As importantly, the site of the lesion, when correlated to the mechanical environment to which the bone is subjected, emphasizes that the pathology predominates in areas of least strain, not those areas subject to greatest deformation. Finally, the pathology observed in the two animal models is histologically identical to that which occurs in the human condition, demonstrating the appropriateness of the extrapolation towards the pathogenesis of the human condition. These observations have led to the development of a new hypothesis which holds major implications towards the design and modification of recruit training regimen.

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Summary

Although stress fractures are the military's primary medical concern during recruit training, the pathophysiology of the lesion remains poorly understood. The most accepted etiology is that the stress fracture lesion is the result of fatigue induced microdamage i.e., that repetitive activity generates small fractures in the boney material at those sites which are subject to the greatest strain (Chamay & Tschantz 1972; Burr et al. 1985; Daffner 1978; Leveton 1946; Markey 1987; Matheson et al. 1987; Nussbaum et al. 1988). In turn, these small cracks would accumulate until a fracture is catalyzed, not unlike the breaking of a paperclip. However, as a result of this contract's research effort, a new SFx hypothesis has been formulated which directly countermands this accepted etiology. Not only does this new eticlogy better explain the SFx pathology observed within human biopsies, it provides a unique opportunity to identify those aspects of the training regimen most likely to cause the damage.

The experiments demonstrate that the most extensive boney defects associated with excessive cyclic loading are not those resulting from an actual material "fracture" across the cortex. Instead, the large area of rarefaction, in both the equine and avian model of stress fractures, are a focal area of high boney turnover, dominated by incompleteley infilled haversian systems and resulting in intracortical porosities (Jones et al. 1989; Rubin et al. 1986). Continued abuse may result in material damage (and ultimate failure), but only after the remodeling has compromised the integrity of the tissue.

As surprisingly, the location of this lesion, relative to the distribution of strain generated across the bone during functional loading, correlates best with those areas of the cortex exposed to the lowest strain magnitudes, not those sites subjected to the highest deformations (Rubin et al. 1985, 1989a,b). Based on these preliminary results, we conclude that the boney remodeling precedes the material breakdown, and that the turnover is an "adaptive" response to some undetermined aspect of the loading milieu that is not peak strain magnitude (Rubin et al. 1987).

From this evidence, we conclude that the resorption of the cortex (and the eventual failure of the bone), is a cycle dependent totally resorptive remodeling response stimulated within the bone "tissue", rather than a failure of the bone "material" due to matrix fatigue. The evidence supporting this conclusion is

extensive, and given the cross-species similarities in the pathology, allows for a powerful extrapolation to the human condition. Finally, these observations have led to the development of a new hypothesis which holds major implications towards the design and modification of recruit training regimen:

General Hypothesis: Although cycle dependent, the stress fracture lesion is not a result of accumulated fatigue microdamage, but instead is a very specific and localized remodeling response which occurs at, or near, the neutral axis of loading (the site of least strain deformation). Therefore, we propose the greatest determinant of the SFx lesion to be repetitive cyclic activity, regardless of its intensity. Because the lesion is a remodeling phenomenon, it will occur predominantly in skeletal tissue already involved in boney turnover. Therefore, older skeletons, or skeletons subject to a higher state of intracortical activity (females), are at greater risk of the stress reaction state.

Military Significance

The goal of this research program was to improve our understanding of the mechano-pathophysiology of the stress fracture lesion. Only then can the training regimen be altered to effectively supress those parameters of the functional milieu which exacerbate the condition.

During peacetime, stress fractures are one of the most frequent physical training injuries observed in the U.S. military population (Jones et al. 1989; Schmidt et al. 1982) evident in up to six percent of male (Scully & Besterman 1982), and twenty percent of female basic trainees (Brudvig et al. 1983; Protzman & Griffis 1977). In addition, older recruits (over 21) are more susceptible to this injury than younger trainees (Gardner et al. 1988), yet a history of athletic activity will not necessarily suppress the lesion (Swissa et al. 1989). While this injury is not unique to the Armed Forces of the United States, (Chisin et al. 1987; Giladi et al. 1985; Sugiura et al. 1985), other countries have reported stress reaction incidence in recruits as high as thirty percent (Milgrom et al. 1985a,b). Catastrophically, this incidence will rise in times of war, concurrent to the accelerated induction of trainees (Swissa et al. 1989; Bernstein & Stone 1944). Consequently, this stress reaction jeopordizes not only recruit health, safety and morale, but severely compromises the military's medical and defense resources.

The initial symptoms include a reluctance to bear weight on the affected appendage, and is associated with acute "point pain" on palpation (Floyd et al. 1987; Chisin et al. 1987). These symptoms, although difficult to identify radiographically, coincide with focal areas of increased Technetium uptake evident during gamma scan evaluation, reflecting accelerated bone cell activity (Milgrom et al. 1985c; Zwas et al. 1988; Goldfarb 1988). Avoiding the conservative treatment of rest, the lesion can proliferate to a radiographically visible area of rarefaction (Chisin et al. 1987; Zwas et al. 1987), and continued abuse can engender boney defects such as hairline fractures (Uhthoff & Jaworski 1985), or even complete structural failure (McBryde 1985). However, that the pathology is in fact a response to initially accumulated microdamage has never been established (Harris et al. 1988; Burr et al. 1985). Indeed, as the tibia's physical properties are unchanged (if not improved) following the running of a marathon (Rubin et al. 1987a), it would diminish the likelihood that physiologic levels of loading could engender damage. With as many as 46% of total SFx being reported following only the first week of military training (Gardner et al. 1988) the "accumulated damage" theory is compromised even further, as this is insufficient time to surpass even the most pessimistic projections of bone's fatigue life at physiologic strains (Carter et al. 1981a). Interestingly, it is precisely the time period in which remodeling response could have mobilized osteoclastic resorption of the cortex, and the new bone which is being laid down to replace it has not yet mineralized, and therefore cannot yet supplement the bone's diminished strength.

Without question, stress fractures are the leading cause of time lost in basic training (Scully & Besterman 1982; Leichter et al. 1989). As they require at least 6-8 weeks of rest without weight bearing for adequate healing, they also represent a severe increase in the cost effectiveness of recruit training (Milgrom et al. 1985a; Jones et al. 1989). Unfortunately, attempts to reduce the incidence of this injury have achieved only a limited degree of success (Bensel 1986; Scully & Besterman 1982; Duker 1982). This is largely due to our poor understanding of the mechanical factors (stress, strain, strain rate, strain distribution, number of strain repetitions) which are actually responsible for causing the pathology within the bone tissue (Rubin & Hausman 1988; Brand & Rubin 1988). The objective of the series of experiments reported here was to determine to what extent repetitive cyclic loading, applied within magnitude, manner, and duration parameters

which are relevant to basic training, may be "perceived" by the bone as a resorptive stimulus, the precursor to the stress fracture lesion. The impact of an improved understanding of the stress fracture pathogenesis on the health and well being of the recruit cannot be underestimated.

Final Report of Results

The objective of the contract has been to determine the extent to which excessive repetitive loading at physiologic magnitudes will produce deleterious remodeling within limb bones, ultimately resulting in structural damage. The study was divided into three parts; a) the changes which occur in bone strain distribution concurrent to metabolic fatigue, b) the skeletal remodeling response to excessive repetitive loading, and c) the correlation of the animal pathology with that observed in the human.

In the first objective, the quantification of the strain milieu of the horse cannon bone has allowed us to model the mechanical environment to which bones are subjected during extreme functional activity. This model was chosen as the cannon bone is essentially the only other site, other than those in the human skeleton, in which the stress fracture will occur naturally (Gray & Rubin 1987; Rubin et al. 1989a; Nunamaker et al. 1987; Koblik et al. 1986). By determining the strain milieu to which the cannon bone is naturally exposed, we were able to correlate the site of the pathology with the types and magnitudes of strain to which this area of the bone is subjected (Rubin et al. 1989b). In addition, we were able to determine if this manner of loading was altered following metabolic fatigue (Rubin et al. 1989c).

With the second objective, the use of the externally loadable avian wing preparation has proven very successful in providing us the initial understanding of the etiology of the "stress fracture" condition. Specifically, this animal model has provided unique (albeit controversial) experimental information as to the mechanopathogenesis of the lesion (Jones et al. 1989; Rubin et al. 1984, 1986, Harris et al. 1988). Further investigation, using this in vivo model, has begun to define those components of the functional loading environment which are most potent in their capacity to accelerate intracortical remodeling and therefore the "stress reaction" pathology (Rubin et al. 1984, 1985, 1989b,c). This, in turn, could identify specific exercise regimes which should be amended or avoided in the training program in order to

diminish or eradicate this injury.

Finally, the pathology generated in both the equine and avian models were qualitatively compared to that observed in human biopsy material from the AFIP (Rubin et al. 1986; Harris et al. 1988; Jones et al. 1989). By defining the cross-species similarities in the skeletal tissue response to excessive cyclic loading, a powerful extrapolation to the pathomechanics responsible for the human condition becomes possible.

a) Changes in the Distribution of Skeletal Strain Concurrent to Metabolic Fatigue

The primary objective of this series of experiments was to establish a protocol capable of monitoring changes in the metabolic level of fatigue incurred in the exercising horse, and correlate these changes with any simultaneous alterations in the distribution of strain across the third metacarpal (MCIII).

Our initial hypothesis for the appearance of the lesion was that metabolic fatigue concurrent to extreme levels of exertion would result in the recruitment of new combinations of muscular activity thereby altering the "normal" distribution of strain across the bone. This "new" distribution would in turn stimulate an adaptive remodeling response, and, secondary to the intracortical remodeling, cause the extracellular matrix to fail. However, although achieving numerous indices of metabolic fatigue (i.e. based on VO_2, respiratory quotient, blood lactate), no fatigue-induced shift in the manner of loading at the level of the bone could be observed.

Following acclimation training an a motorized treadmill, eight horses were surgically instrumented, under a general halothane anesthesia and under aseptic conditions, with three rosette bone bonded strain gages. Through a medial and cranio-lateral incision, three, three-element rosette strain gages were attached to the surface of the medial, cranial, and lateral aspects of the diaphyseal midshaft of the cannon bone (MCIII). This was performed by removal of one square centimeter of periosteum, and degreasing the bone with anhydrous ether. The gages were then attached using 2-isobutyl cyanocrylate, and strain relief flanges screwed to the bone, approximately 2 centimeters from the gage site, to minimize tension on the lead wires. All wounds were then sutured closed, and the limb bandaged (Rubin et al. 1989b,c). Gage locations and geometric properties of the cannon bone were determined using radiographs and computer aided tomography (CAT scanning) respectively. As the trauma to the animal was minimal,

a full exercise protocol was possible the following day.

Three three-element rosette gages, generating nine channels of strain data from the bone, give direct indications of the magnitude of strain generated on the bone's surface as a result of activity. The "raw" strain from each gage is analyzed to give principal strains from the three gage locations, and allows for the calculation of distributions of principal strain, normal strain, shear strain, and strain energy density across the bone. We have monitored these distributions such that any changes concurrent to the onset of metabolic fatigue would be observed.

Prior to this work, the analysis of bone strain has been limited to those which occur along the bone's material coordinate system (longitudinal) and, therefore, may 'overlook' other relevant strain parameters such as the principal strain orientation and the distribution of shear strain (Carter et al. 1981b). Essentially, this analysis provides a detailed mechanical profile of the bone through a cortical cross section, at any point in the stride and through a series of strides at any given speed. For purposes of this study, a series of twenty strides were interpolated from each steady-state condition to create a single representative average stride. At ten points through the averaged stance phase, principal strains were calculated for each rosette gage site, and a distribution of normal and principal strains across the cortex determined using simple beam theory. Subsequently, using finite element analysis and iterative processing, the distribution of shear strains were calculated through the stride.

The analysis also determines the strain energy density, which represents those areas of the cortex which undergo the greatest level of "work." This is important as high levels of shear may correspond to low levels of normal strain, and vice versa. This calculation has allowed us to identify those areas that see the greatest (and least) strain distortions during activity. If the stress fracture lesion were generated by high levels of microdamage, they would predominate in the site of the cortex subjected to either highest normal strain, shear strain, or strain energy density.

As examples of these calculations, we can show the distribution of normal strain generated during a trot at 6.5 m/s. At the peak strain magnitude of the stance phase, the normal strain distribution shows a strain magnitude of 2459 microstrain on the medial cortex (fig. 1a), with the neutral axis of strain running through the lateral cortex. Given only this plot, it is

possible only to consider the strains represented by these normal strains, i.e., strains at the neutral axis are zero. However, this calculation is not sensitive to the deformation caused by shear. With the calculation allowed by the three rosette gages, a shear distribution can be established (fig. 1b). This demonstrates, at each location within the cortex, the levels of shear that the bone is subjected to. In this case, shear strains of 1889 microstrain are attained, the location of which are well removed from the site of peak normal strains. As bones do not normally fail under compressive strains, but rather to shear strains due to bending and torsion, i.e. the yield to failure in shear is approximately 40% that of compression (Hayes & Snyder 1981), and much smaller shear strains could have a very significant and deleterious effect on the structural integrity of the skeleton.

A final calculation derived from the raw strain recordings is the product of normal and shear strains to create the "strain energy density" (fig. 1c). This analysis identifies those locations in the bone that are subjected to the highest (and lowest) magnitudes of deformation, regardless of their origin.

In figures 1a through c, the complete mechanical milieu generated on the cortex is demonstrated for a specific time period in a stride taken at a certain speed. This manner of loading, either through the stride of speed range, changes very little (Gray & Rubin 1987). What is of critical importance is that the areas of greatest normal strain, shear strain and/or strain energy density in the horse cannon bone are also the areas of the cortex that have the least remodeling activity. Indeed, the most common quadrant in which stress fracture lesion appears, the Antero-lateral cortex (Koblick et al. 1986; Nunamaker et al. 1987), is the area of the cortex exposed to the least strain, be it normal, shear or strain energy density. What this extensive analysis has provided, therefore, is not only direct correlation between presence of the stress fracture lesion and the site of lowest normal strain, but emphasizes that the lesion also appears in the area of least shear and "total" strain. This emphasizes that the stress fracture lesion is not a product of accumulated damage or material breakdown, but is a by-product of a loading environment that sees high numbers of cyclic load reversals, with the pathology occurring at sites of the smallest deformations (Rubin et al. 1984, 1986, 1989a,b).

It has also been proposed that, if metabolic fatigue is incurred, new muscle recruitment patterns would be stimulated and

result in different bone loading patterns to which the bone is not able to resist (Rubin et al. 1989c). To determine if changes in the distribution of strain within the bone will parallel exercise induced changes of the respiratory/cardiovascular system, we monitored alterations in strain patterns concurrent to a series of metabolic indices of fatigue. To achieve this correlation, oxygen consumption, heart rate, and venous lactate concentration were obtained through respiratory gas measurements and blood samples drawn while the animal was exercising. A plateau in the oxygen consumption of an animal is an objective indicator of maximal aerobic power (Maclaren et al. 1989). The ratio of carbon dioxide production to oxygen consumption (respiratory quotient, RQ) indicates the extent to which respiration can provide the energy requirements of the animal, and values greater than 1.2 indicate a substantial reliance of anaerobic metabolism. Similarly, an abrupt increase in blood lactate levels indicates increased anaerobic activity. An RQ over 1.2, with a maximal heart rate, maximal oxygen consumption, and an abrupt increase in lactate levels are the standard clinical signs of metabolic fatigue.

A standard metabolic fatigue test regimen for horses was used, entailing one minute interval training at 4.5, 5.5, 6.5 and 9 meters/sec with the animal running on a 10% incline on a motorized treadmill. In this study, all metabolic tests were run on the animals both before and following surgery. Presurgery, heart rate reached its maximum value during the 5.5 m/s interval and oxygen consumption reached a plateau during the 6.5 m/s interval. Following 45 seconds at 9 m/s canter, RQ exceeded 1.2, max VO_2 had begun to decline, and lactate levels increased significantly, demonstrating that the animal had reached a definite state of metabolic fatigue (fig. 2). This also corresponded to an apparent loss of coordination of the animal and unwillingness to continue running on the treadmill. Following surgery, none of these values changed significantly indicating that the surgical procedure did not diminish the animal's performance.

If fatigued muscle groups had engendered new recruitment patterns, then a new strain distribution would result in the initiation of remodeling activity. As the first step of remodeling activity is the resorption of bone, the initiation of extensive remodeling could lead to bone failure. Comparing the distributions of normal strain, shear strain, and strain energy density for the peak load condition of both pre- and post-fatigue conditions, only very subtle changes in the physical milieu of the bone could be identified (fig. 2). This data demonstrates that

there are no alterations in the manner of loading of the bone with the onset of metabolic fatigue. The work reported here does not support our original hypothesis, and emphasizes that alternative etiologies be considered for the occurrence of such fractures.

What has been demonstrated from these studies, however, is that the area of the cortex which experiences the SFx pathology does not experience high levels of any sort of strain. It must be emphasized that this location is well below any threat of yield failure, and there are many areas of the cortex subject to much greater magnitudes of strain. Therefore, an explanation of the SFx must not depend on magnitude of strain, but by the manner in which it is loaded. In other words, the fracture, although ultimately caused by a material breakdown, is not initiated by damage but by remodeling. It would appear the lesion is secondary to a cycle dependent tissue response to the loading environment. Perhaps this low deformation area is also the site of extremely poor fluid flow or supressed tissue perfusion, concurrently minimizing components of a streaming potential or causing poor nutritive exchange and hydration. Mechanisms aside, the correlation of low strain energy density to the stress fracture lesion would dismiss material failure per se, and requires other pathogeneses, such as the minimal fluid exchange which occurs in this area, to be proposed as responsible for the pathology.

In summary, these locomotor experiments have correlated the lesion to the area where both the normal strain and shear strain is low, and the resultant strain energy density is smallest, diminishing the possibility that the lesion is a result of accumulated microdamage. In addition, metabolic fatigue does not induce a new loading environment, diminishing the possibility that the remodeling observed at the lesion site was stimulated by "adaptation" to a new loading environment. Therefore, we conclude that something about the specific cyclic loading environment that has little to do with fatigue microdamage itself stimulates focal and deleterious remodeling, which secondarily leads to structural failure.

b) Skeletal Remodeling Response to Excessive Repetitive Loading

The primary objective of this series of experiments was to correlate the adaptive tissue pathology which are stimulated by physiologically relevant magnitudes, rates, and durations of applied dynamic loading. This protocol exploits an established in vivo model developed to monitor the remodeling activity in bone

generated by specific, controlled mechanical stimulation.

To investigate the mechanopathogenesis of stress fractures induced by high repetitions of a uniform exercise regime, we utilized the functionally isolated in vivo avian wing preparation previously reported (Rubin & Lanyon 1984, 1985, 1987). With this model, controlled intermittent loads from a modified Instron machine can be applied to the functionally isolated ulna via transfixing pins. The loads of the servohydraulic actuator can be adjusted to produce peak longitudinal strains at the midshaft from a range of 500 to 4000 microstrain, levels determined to be physiologic when compared to strains measured from a variety of skeletal locations during activity (Rubin & Lanyon 1982). In this protocol, the applied strain waveform was sinusoidal with a maximum loading and unloading rate of 50,000 microstrain/sec., also physiologic in magnitude. Each ulna preparation was subjected to regimes up to as many as 30,000 cycles/day, over a single period of loading, for five days/week. Loading was discontinued either when the animals showed discomfort or at 8 weeks, whichever was the sooner.

The maximum effect of an osteogenic mechanical stimulus was generated following only a very short exposure to an intermittent load regime (thirty-six load reversals), increased cyclic loading by a factor of fifty did not stimulate additional bone formation (Rubin & Lanyon 1984). The importance of the dynamic state was also demonstrated, static load regimes, applied at similar strain magnitudes, were ignored as an osteogenic stimulus, and osteoporosis was generated (Lanyon & Rubin 1985). Following these observations, the avian wing preparation was loaded for 100 cycles/day to determine the role of strain magnitude as an osteogenic stimulus (Rubin & Lanyon 1987). The amount of new bone formed was directly proportional to the magnitude of the engendered strain. This dose-response phenomenon produced essentially no new bone at 1,000 microstrain, yet was sufficient to inhibit the osteoporotic response. A 15-23% increase in bone cross-sectional area was stimulated at 2,000 microstrain, and a 28-42% increase in new bone at 3,000 microstrain. These experiments emphasize that the osteogenic stimulus can be triggered by very few cycles of a dynamic load regime, but for the stimulus to be adaptive it need not be hyperphysiologic in amplitude.

In the series subjected to excessive repetitive cyclic loading (30,000 cycle/day series; animal number = 28), a similar increase in bone cross-sectional area was elicited, suggesting that the

cells responsible for new bone formation had been stimulated to work at their peak capacity by exposure to the first "few" loading repetitions. However, while microradiographs of the ulna midshaft from the 100 cycles/day animals demonstrated the degree of intracortical remodeling series to be very low, in the 30,000 cycles/day series the intracortical remodeling was extensive (Rubin et al. 1984, 1986; Jones et al. 1989). This would suggest that two separate and distinct mechanisms exist; one responsible for bone modeling (new bone formation), and one for bone remodeling (intracortical tunneling). Interestingly, the large structural defects which were apparent in the bone cortices were NOT cracks or microdamage, but rather the area of rarefaction consisted of resorption spaces and expansion of vascular channels. Th se studies represent in vivo remodeling data in response to cyclic loading of up to 1.5 million cycles without failure of the preparation. Even under these extreme conditions, there was no sign of extracellular tissue damage whatsoever, only an increase in focal intracortical turnover. These spaces, combined with the exuberant periosteal new bone formation with which they were associated, presented a remarkably similar appearance to the stress fracture pathology observed in the human material (Harris et al. 1988).

To correlate the pathology to the applied mechanical milieu, strain gage studies (similar to those described above) were performed to establish the specific distribution of applied strains. As was the case with the equine pathology, the region of the cortex which contained the most consistent, extensive intracortical remodeling was not that subjected to the greatest strain (the area of the cortex most likely to accumulate microdamage), but rather was located about the bone's neutral axis, the area of the cortex subjected to the SMALLEST normal strains (fig. 3a).

Using the rigorous mechanical analysis developed for the cannon bone study, it was also possible to calculate not only the normal strain distribution, but the shear strain distribution and strain energy density (fig. 3b&c). This analysis emphasizes that the location of the stress fracture lesion in the bird ulna appears within the area of the cortex within the smallest strain deformation, not the areas subject to high magnitudes. As in the horse study, the stress fracture lesion appears at a site of minimal shear and strain energy density, emphasizing the observation that the response was triggered by some aspect other than material microdamage (Rubin et al. 1990).

c) Correlation of Animal Models to Human Pathology

The primary objective of this series of experiments was to correlate the pathology observed in the human condition to that engendered in the animal models, thereby providing a basis of extrapolation from one species to another. During the period of the contract a large collection of human "stress fracture" or "stress reaction" material was reviewed at the Armed Forces Institute of Pathology in Bethesda, Md. (Harris et al. 1988). Of one hundred and twenty-one cases thus coded, sixty-one had sufficient historical, radiographic, and histologic materials to permit fitting into a time oriented sequence. Unfortunately, the functional strain levels to which these cases were exposed remains a matter of conjecture since exact exercise regimes were seldom available from the historic material.

In these clinical cases, frank stress fractures were distinctly in the minority. Where they occurred, the changes seen radiographically and histologically were compatible with the duration of fracture repair delineated by the case report. Of great relevance to this experimental protocol were the cases of "stress reaction" that were biopsied prior to any evidence of gross structural failure. In these cases, the cortical remodelling and periosteal and endosteal new bone formation was very similar to the histologic changes observed in the avian model, particularly those avian subjects whose loading history was of several weeks duration. (The histologic findings of the human biopsy data, and their correlation to the animal studies, is reviewed in depth in the recent publication of Jones et al , 1989). While there was marked deposition of periosteal new bone formation (perhaps accounting for the increase in Technetium uptake seen in other studies; Giladi et al. 1985; Milgrom et al. 1985b), there was virtually an absence of extracellular matrix microdamage. Instead, focal areas of intracortical remodeling was widely apparent, which appeared to coalesce into a trans-cortical lesion. Indeed, it would appear that the tissue was adapting in response to a "non-destructive" stimulus, a reparative "reaction" to accumulated damage was absent.

Given the stark similarities between the pathology observed in the clinical presentation of training-induced stress fractures and that demonstrated in both the equine and turkey models, an extrapolation from the quantified mechanical milieu of the animal studies to that unquantified situation in the human seems warranted. Indeed, we would conclude, based on the integration of

these three studies, that the lesion in the human is a result of an aberrant remodeling stimulus, driven not by a pressure to repair extracellular matrix damage, but somehow influenced by the cyclic nature of the signal which stimulates resorptive remodeling activity.

Discussion

The etiology of the stress fracture condition has been considered previously to be the result of fatigue (Markey 1987; Carter et al. 1981a; Burr et al. 1985). As in the breaking of a paper clip by repeated bending, the stress fracture lesion in the bone cortex has been thought to be generated by accumulation of fatigue microdamage. However, the controlled loading environment made possible by the avian preparation, and corroborated by the correlation of the equine lesion to its functional milieu, emphasizes that the most extensive and demonstrable bone defects associated with excessive repetitions of cyclic loading are not those resulting from an actual "fracture" across the material, but rather a large area of rarefaction, resulting from cellular resorption, which inevitably leads to both pain and structural failure.

As importantly, the lesions produced by loading the avian model do not occur in the area of the cortex subjected to the highest strains, but rather, these lesions occur predominantly in the area of the bone where the bone's strain energy density, as well as normal and shear strains, are least. Transposition of the strain gauge data, derived from the horse metacarpal even following metabolic fatigue, demonstrates that naturally occurring stress fractures will also occur in the region of lowest strain history. Extrapolation to the human (an exercise supported by the cross-species similarities evident in the pathology), would suggest that the human condition is also a result of an adaptive response to some aspect of cyclic loading, and is not dependent on microdamage.

In both the natural and the artificially induced lesions, there is sub-periosteal and sub-endosteal new bone formation adjacent to the most marked intracortical lesions. That this new bone formation has had sufficient time to mineralize supports the concept that the remodeling was stimulated from the onset of loading, and was not generated subsequent to accumulated damage. These lesions are commonly characterized by a defect of less well

mineralized tissues stretching from one surface of the original cortex to the other. As demonstrated by microradiography, the lesion is not a distinct crack, but rather a large area of rarefaction caused by substantial intracortical remodelling. Considering both the presence of new bone and the areas of porosity within the cortex, we feel strongly that this "stress fracture" reponse should not be considered as a "failure of the material", but rather an adaptive remodelling response of the tissue to some cycle dependent aspect of the strain milieu, the CONSEQUENCE of which is the "stress fracture" lesion. The resorption of the cortex and the eventual failure caused by the decrease in effective load bearing area are thus more likely to be a cyclically engendered remodelling response within the bone "tissue," rather than a strain engendered fracture of the bone "material" due to fatigue. By continuation of this contract, we believe it would be possible to further define those aspects of the strain milieu which are responsible for the deleterious remodeling, and establish modes of loading which may supress this condition. It may also be possible to identify specific population subgroups who may be more susceptible to the SFx pathology because of their already accelerated intracortical activity within their skeletal tissue.

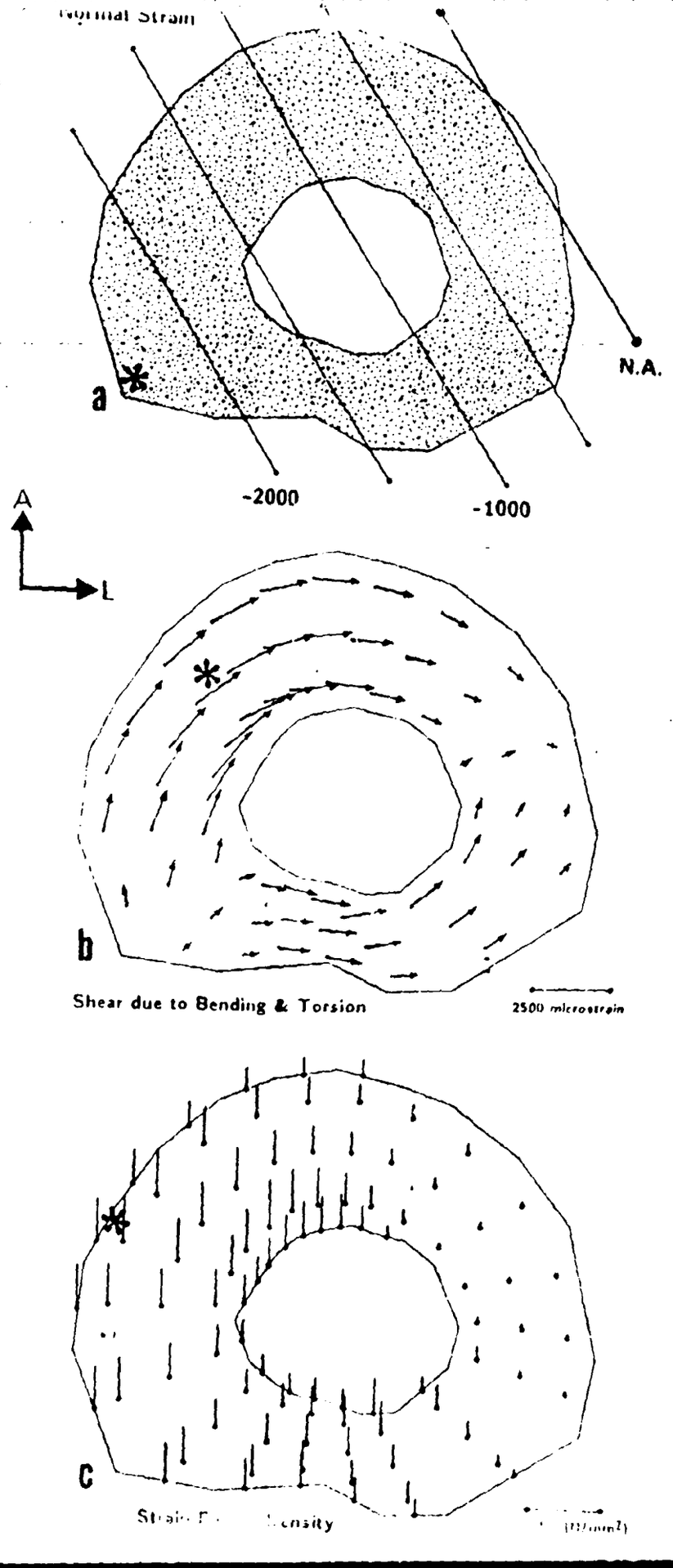
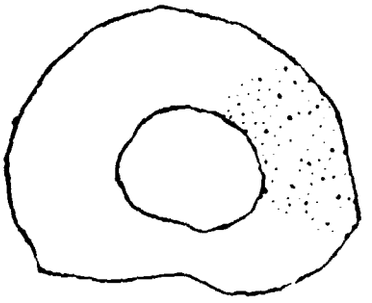


Fig. 1 The distribution of strain generated in the thoroughbred horse cannon bone during a 6.5 m/s trot is shown in diagrams a-c. The normal strain distribution (a) shows the highest longitudinal strain magnitudes occur in the medial-posterior cusp (*) of the cortex. The shear due to both bending and torsion (b) demonstrate the highest shear to occur within the medial cortex (*). Finally, the strain energy density (c) shows the highest total deformation to occur on the medial ridge of the bone. Interestingly, over 90% of the stress reaction injuries in the thoroughbred racehorse occur within the lateral region of the cortex, the area of the bone subjected to the lowest strain (shaded region in inset below).



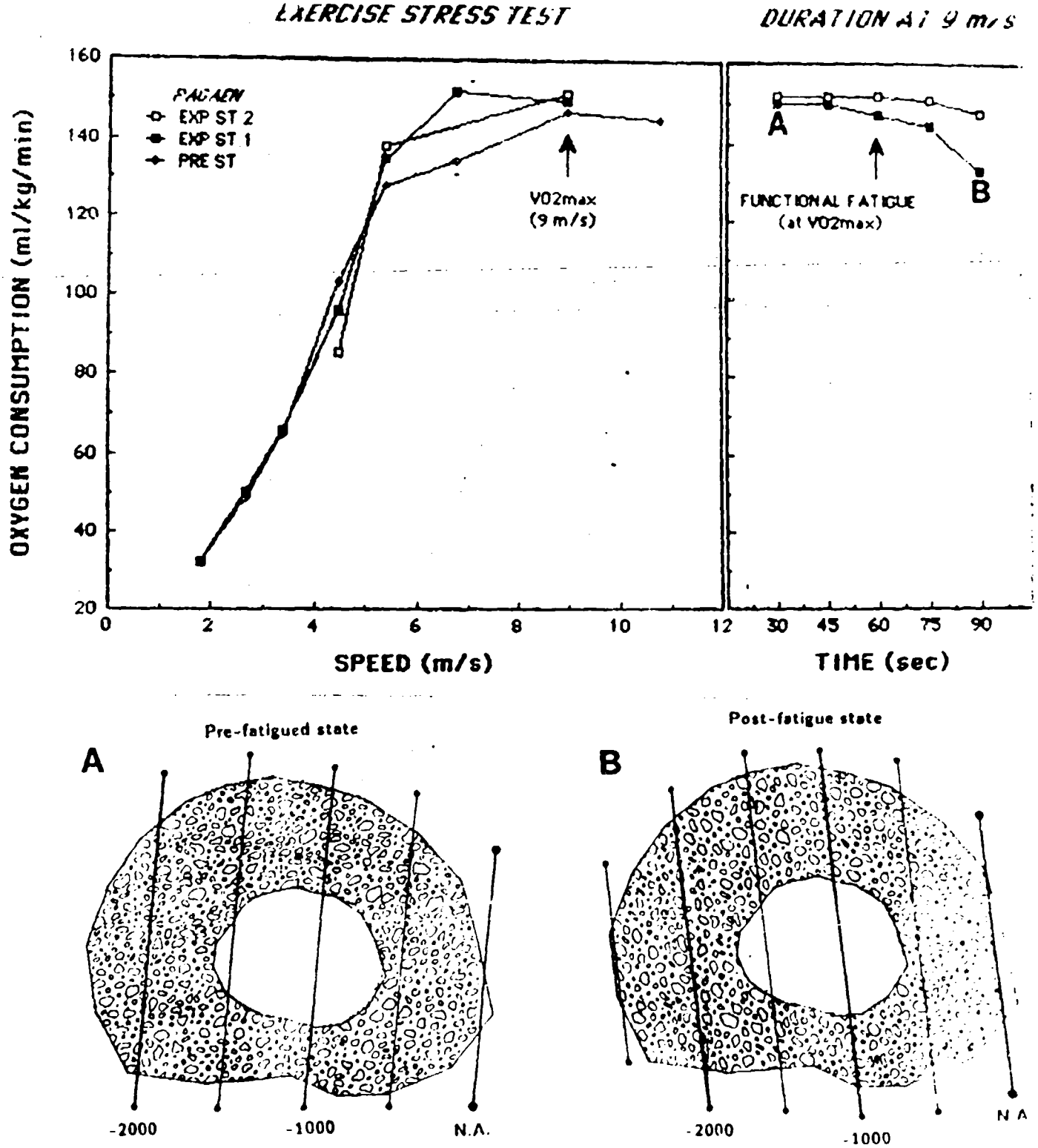
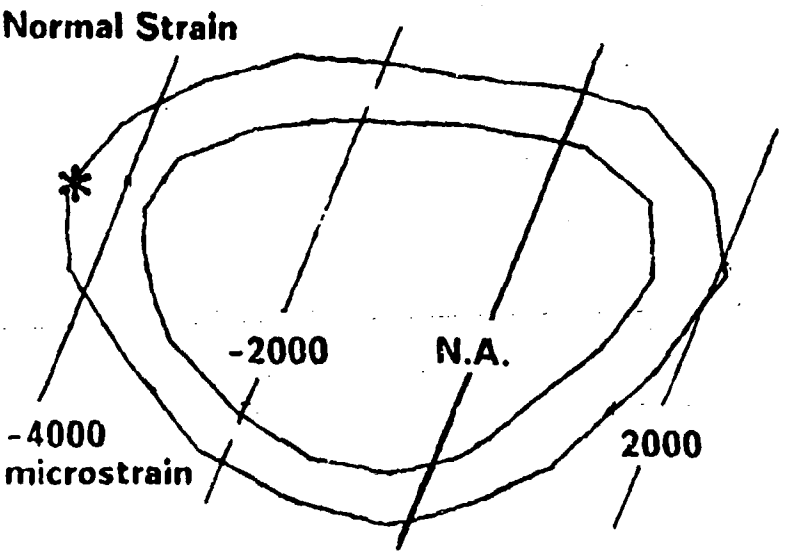
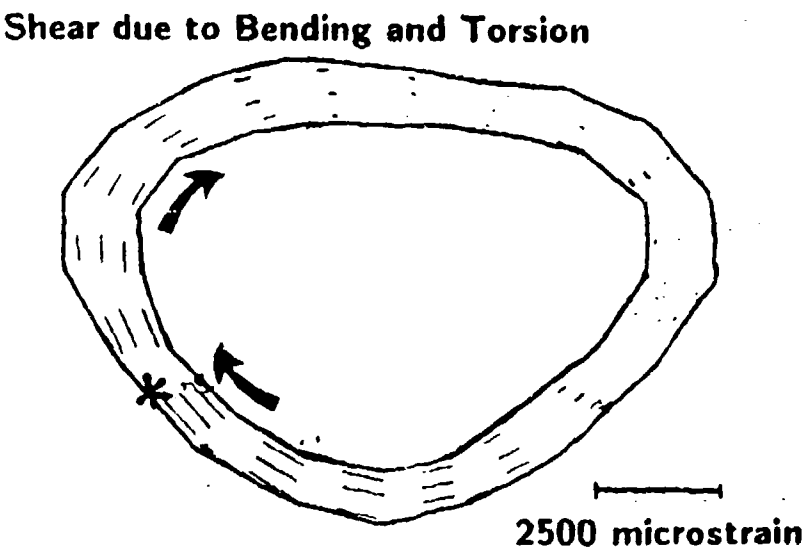


Fig. 2 Oxygen consumption was measured in the exercising horse while running on a 10% inclined motorized treadmill (top). The normal strain distribution generated at 9 m/s prior to metabolic fatigue (site A) shows the neutral axis of loading to cross through the lateral cortex of the cannon bone (lower left). Following metabolic indices of fatigue (decrease in VO_2 max), the strain distribution generated at the same speed (site B) remained essentially unchanged (lower right).





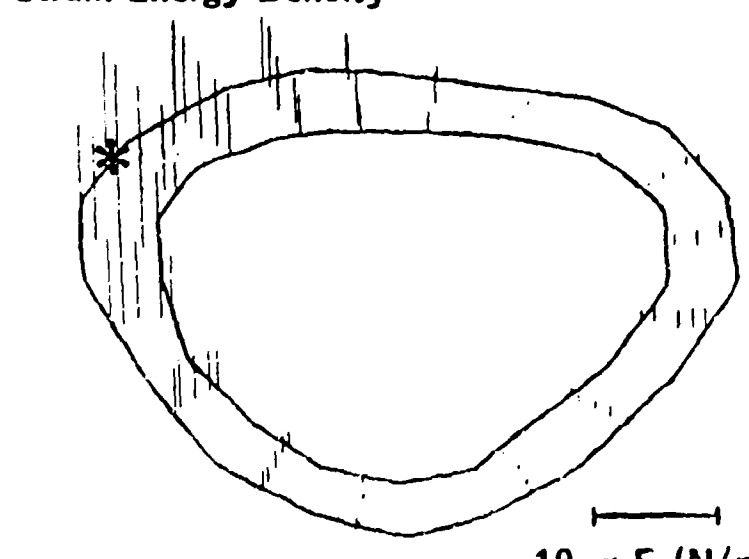
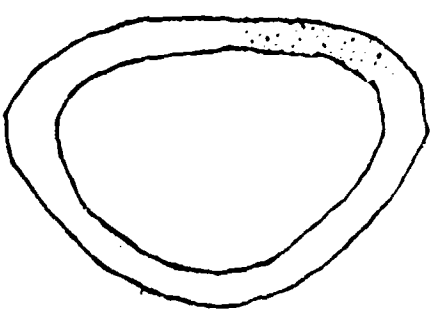


Fig. 3 For the loaded ulna preparation, the distribution of normal strain (top), shear strain (center), and the product of their deformation, strain energy density (bottom), are shown for a case of 1050 Newtons of axial load. In each case, the site of highest magnitude is given (*), and is well removed from that area of the cortex in which the stress fracture lesion appears (shaded below).



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